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(54) SKIN BLEACHING COMPOSITION

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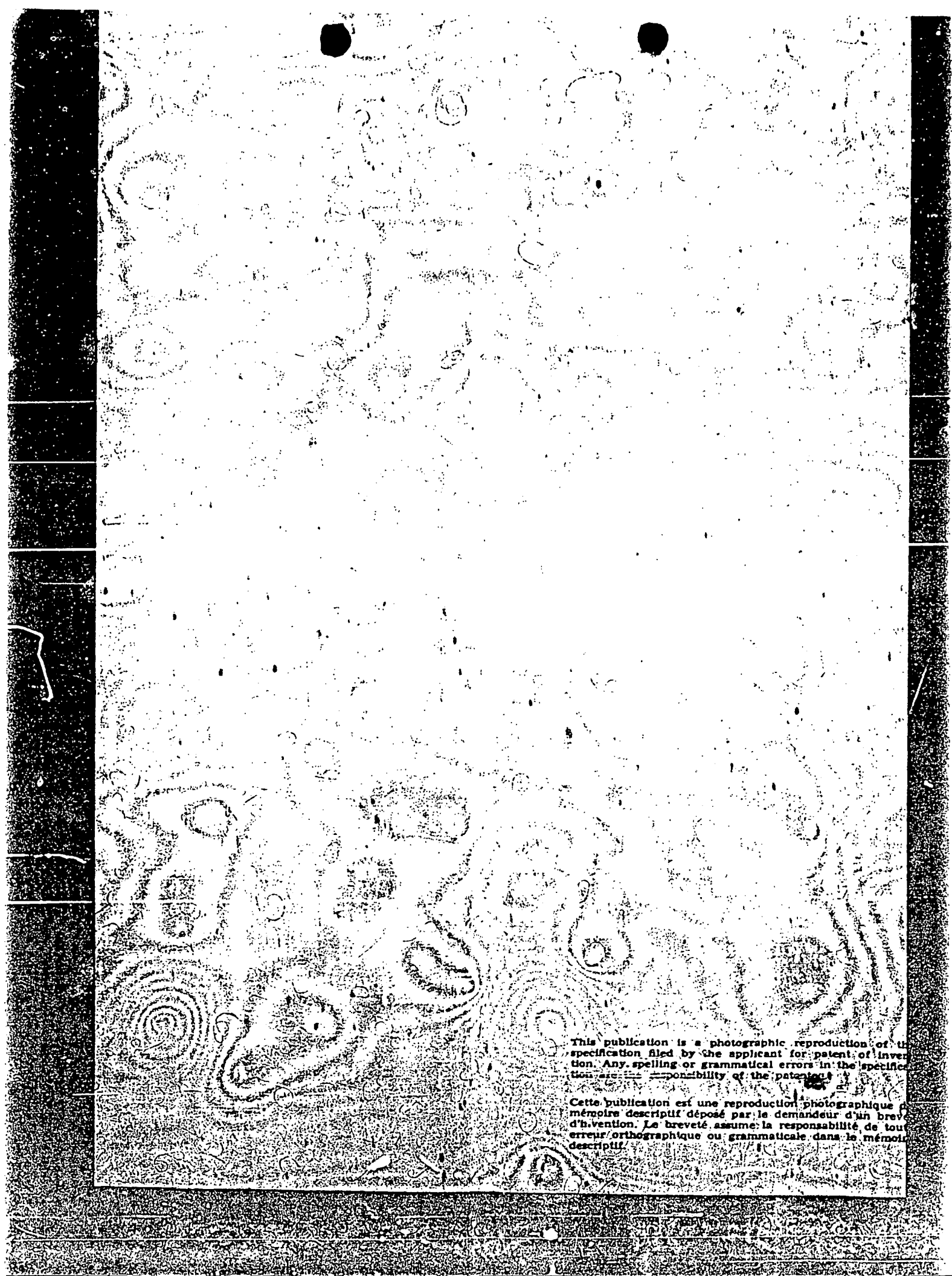

SKIN BLEACHING COMPOSITION

Abstract of the Disclosure

A synergistic skin-bleaching composition for use by topical application has been found which comprises a mixture of a bleaching agent, a skin irritant-exfoliating agent and an anti-inflammatory agent formulated in a pharmaceutically-cosmetically acceptable vehicle. The composition comprising 2% hydroquinone, 0.05% retinoic acid and either 0.025% dexamethasone or fluorometholone was particularly effective.

Background of the Invention

1) Field of the Invention: This invention relates to a new synergistic skin-bleaching composition for use by topical application.

2) Description of the Prior Art: So-called compositions for the bleaching of skin have been known for many years, if not centuries. The prior art contains many references to the use of hydroquinone and its derivatives as agents in bleaching creams, etc., the most pertinent of which are:

a) U. S. Patent No. 3,060,097, issued October 23, 1962 to a skin-bleaching composition comprising sodium hypochlorite, hydroquinone monobenzyl ether and a "penetrant". Three British Patents No.'s 763,029, 855,431 and 965,869 issued to the same inventor on similar compositions.

b) French Patent No. 1,513,395, issued January 8, 1968 to a skin-bleaching composition comprising hydroquinone monobenzyl ether or a derivative thereof in combination with tyrothricin or a derivative thereof.

c) French Patent No. 1,270,854, issued July 24, 1961 to

a skin-bleaching composition comprising hydroquinone benzyl ether (l'ether de benzylhydroquinone) and an anti-oxidant. The product may be formulated to contain vitamins, amino acids, cholesterol, etc.

d) United States Patents No.'s 2,274,725 (March 3, 1942), 2,376,884 (May 29, 1945) and 2,377,188 (May 29, 1945) are to sun-screen preparations comprising hydroquinone as the active sun-filter agent. These preparations are stabilized by the addition of certain anti-oxidants.

e) Zschr. Haut-Geschl.-Krkh. 42, 17: 711-716 reports studies of bleaching the skin using hydroquinone monobenzyl ether. When a subject was found to have sensitive skin, 5% hydroquinone monobenzyl ether and 4% prednisolone was used to prevent or control the contact dermatitis produced by the hydroquinone monobenzyl ether. No mention is made of an improved bleaching effect when the preparation contained prednisolone.

f) Some other articles reporting on skin-bleaching by the use of hydroquinone or its derivatives are:

1. Archives of Dermatology, 84, No. 1, 131-134 (July 1961).
2. Clinical Medicine, 70, No. 6, 1111-1114 (June 1963).
3. Clinical Medicine, 73, No. 3, 87-88 (March 1966).
4. Postgraduate Medicine, 37, No. 2, 198-201 (February 1965).
5. J. Investigative Medicine, 18, 119-135 (1952).
6. J. Am. Medical Assoc., 152, No. 7, 577-582 (June 13, 1953).
7. Dermatologica, 134, 125-128 (1967).
8. Archives of Dermatology, 93, No. 5, 589-600 (May 1966).

The above cited art constitutes but a small portion of the prior art but is representative of that deemed most pertinent. None of the above teaches or anticipates the three component synergistic compositions of the present invention.

Summary of the Invention

A synergistic skin-bleaching composition for external application has been found comprising a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monoethyl ether and hydroquinone monobenzyl ether, a skin irritant-exfoliating agent and an anti-inflammatory corticosteroid.

Complete Disclosure

It has long been desirable in certain skin disorders or diseases to be able to depigment (bleach) the skin to remove certain disfiguring blemishes generally caused by the deposition of excess quantities of melanin. This hyperpigmentation is generally viewed as cosmetically undesirable or phychologically disabling. Examples of these blemishes would be freckles, senile lentigo, lentigines (liver spots), melasma, contact allergy pigmentation, sunburn pigmentation, post-inflammatory hyperpigmentation due to abrasion, burns, wounds, dermatitis, phototoxic reaction and other similar small, fixed pigmented lesions. Likewise, it is also desirable to be able to decolorize normally pigmented skin to generally increase "fairness" of appearance and to blend hypopigmented areas into surrounding bleached skin. This is particularly so in the treatment of negroes, brown-skin people, or generally dark skinned people suffering from vitiligo.

It was an object of the present invention to prepare an

effective and superior product as compared to those currently on the market or known in the literature.

The compounds hydroquinone, hydroquinone monomethyl ether, hydroquinone monobenzyl ether, ammoniated mercury, zinc peroxide, red mercuric oxide, sodium hypochlorite, hydrogen peroxide, mercurous chloride and bichloride of mercury are all known in the literature as bleaching agents of the skin. Only hydroquinone is recognized as a bleaching agent possessing satisfactory qualities.

The object of the present invention has been achieved by the formulation of a superior synergistic skin-bleaching composition for external application which comprises a mixture of a bleaching agent, a skin irritant-exfoliating agent and an anti-inflammatory agent in a pharmaceutically-cosmetically acceptable vehicle.

A preferred embodiment of the present invention is a synergistic skin-bleaching composition for external application comprising a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monoethyl ether and hydroquinone monobenzyl ether, a skin irritant-exfoliating agent and an anti-inflammatory corticosteroid formulated in a pharmaceutically-cosmetically acceptable vehicle.

Another preferred embodiment is a synergistic skin-bleaching composition for external application comprising about 1% to about 10% of a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monoethyl ether and hydroquinone monobenzyl ether, and about 0.025% to about 80% of a skin irritant-exfoliating agent and about 0.01% to about 3.0% of an anti-inflammatory corticosteroid formulated in a pharmaceutically-cosmetically acceptable vehicle.

Another preferred embodiment is a synergistic skin-bleaching

composition for external application comprising about 1% to about 5% of a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monoethyl ether and hydroquinone monobenzyl ether, about 0.025% to about 15% of a skin irritant-exfoliating agent selected from the group comprising unsaturated fatty acids, long chain fatty acid esters or salts thereof, retinoic acid, oleic acid, arachidonic acid, polyoxyethylene lauryl or myristyl ethers, alkylamines containg 5 to 16 carbon atoms, salicylic acid and benzoic acid, and about 0.01% to about 3.0% of an anti-inflammatory corticosteroids selected from the group comprising hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone, betamethasone, fluocinolone acetonide, triamcinolone, fluocinolone, triamcinolone acetonide, methylprednisolone, fluorometholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.

A more preferred embodiment is a synergistic skin-bleaching composition for external application comprising about 1% to about 5% of hydroquinone, about 0.020% to about 10% of a skin irritant-exfoliating agent selected from the group comprising retinoic acid, arachidonic acid, oleic acid, linoleic acid, linolenic acid, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, polyoxyethylene lauryl ether, polyoxyethylene myristyl ether, salicylic acid, benzoic acid, and n-octylamine, and about 0.01% to about 3% of an anti-inflammatory corticosteroid selected from the group comprising dexamethasone, betamethasone, fluocinolone, fluocinolone acetonide, triamcinolone, hydrocortisone, triamcinolone, acetonide, fluorometholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.

A most preferred embodiment is the synergistic skin-bleaching

composition for external application comprising about 2% hydroquinone, about 0.05% retinoic acid and about 0.025% fluocinolone formulated in a pharmaceutically-cosmetically acceptable vehicle.

Another most preferred embodiment is the synergistic skin-bleaching composition for external application comprising about 2% hydroquinone, about 0.05% retinoic acid and about 0.025% dexamethasone formulated in a pharmaceutically-cosmetically acceptable vehicle.

Still another most preferred embodiment is the synergistic skin-bleaching composition for external application comprising about 2% hydroquinone, about 0.05% retinoic acid and about 2.5% hydrocortisone or hydrocortisone acetate formulated in a pharmaceutically-cosmetically acceptable vehicle.

A preferred embodiment of the present invention is a method of bleaching human skin by applying to the skin a synergistic skin-bleaching composition which comprises a mixture of a bleaching agent, a skin irritant-exfoliating agent and an anti-inflammatory agent formulated in a pharmaceutically-cosmetically acceptable vehicle.

Another preferred embodiment is the method of bleaching human skin wherein the bleaching composition comprises a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monoethyl ether and hydroquinone monobenzyl ether, a skin irritant-exfoliating agent and an anti-inflammatory corticosteroid formulated in a pharmaceutically-cosmetically acceptable vehicle.

A further preferred embodiment is the method of bleaching human skin wherein the bleaching composition comprises about 1% to about 10% of a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone

monoethyl ether and hydroquinone monobenzyl ether, and about 0.025% to about 80% of a skin irritant-exfoliating agent and 0.01% to about 3.0% of an anti-inflammatory corticosteroid formulated in a pharmaceutically-cosmetically acceptable vehicle.

A more preferred embodiment is the method of bleaching human skin wherein the bleaching composition comprises about 1% to about 5% of a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monoethyl ether and hydroquinone monobenzyl ether, about 0.025% to about 15% of a skin irritant-exfoliating agent selected from the group comprising unsaturated fatty acids, long chain fatty acid esters or salts thereof, retinoic acid, arachidonic acid, polyoxyethylene lauryl or myristyl ethers, oleic acid, alkylamines containing 5 to 16 carbon atoms, salicylic acid and benzoic acid, and about 0.1% to about 3.0% of an anti-inflammatory corticosteroids selected from the group comprising hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone, betamethasone, fluocinolone acetonide, triamicinolone, fluocinolone, triamcinolone acetonide, methylprednisolone, fluorometholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.

Another more preferred embodiment is the method of bleaching human skin wherein the bleaching composition comprises about 1% to about 5% of hydroquinone, about 0.020% to about 10% of a skin irritant-exfoliating agent selected from the group comprising retinoic acid, arachidonic acid, linoleic acid, oleic acid, linolenic acid, sodium lauryl sulfate, dioctyl sodium sulfosuccinate, polyoxyethylene lauryl ether, polyoxyethylene myristyl ether, salicylic acid, benzoic acid, and n-octylamine, and about 0.01% to about 3% of an anti-inflammatory corticosteroid selected from the group comprising dexamethasone, betamethasone, fluocinolone, flucinolone

acetonide, triamcinolone, hydrocortisone, triamcinolone acetonide, fluoromethalone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.

A most preferred embodiment is the method of bleaching human skin wherein the bleaching composition comprises about 2% hydroquinone, about 0.05% retinoic acid and about 2.5% hydrocortisone or hydrocortisone acetate formulated in a pharmaceutically-cosmetically acceptable vehicle.

A most preferred embodiment is the method of bleaching human skin wherein the bleaching composition comprises about 2% hydroquinone, about 0.05% retinoic acid and 0.025% fluorometholone formulated in a pharmaceutically-cosmetically acceptable vehicle.

Another most preferred embodiment is the method of bleaching human skin wherein the bleaching composition comprises about 2% hydroquinone, about 0.05% retinoic acid and 0.025% dexamethasone formulated in a pharmaceutically-cosmetically acceptable vehicle.

Hydroquinone, hydroquinone monomethyl ether and hydroquinone monobensyl ether are all known in the literature as bleaching agents for lightening of the skin. While there is some question as to the mode of action of these agents and treatment is considered an "art" rather than a science, it is generally thought that all of these agents work through the common intermediate hydroquinone. Additionally, it is known that hydroquinone is the least irritating of these hydroquinones, the ethers generally having the reputation of causing various types of dermatitis. It is also known that the ethers are unpredictable in their bleaching effect and sometimes cause a progression of depigmentation after application has been stopped. Hydroquinone is the agent of choice when a hydroquinone bleaching

agent is desired for these reasons.

A 2% hydroquinone composition is commercially available under the tradename Eldoquin and Eldopaque by Paul Elder & Company. Hydroquinone is reported to be the sole active ingredient.

In our hands, it has been found that a preparation containing only 2% hydroquinone is unpredictable and not always effective. Similar results have been reported in the literature (Clinical Medicine, 73, No. 3, 87-88 [March 1966]) wherein 35% of those subjects treated showed excellent results, 5% good, 35% fair and 25% poor.

Subsequent investigations to improve these results were undertaken and it has been unexpectedly found that a composition containing hydroquinone, or a derivative thereof, in combination with a skin irritant-exfoliating agent and an anti-inflammatory corticosteroid produced good to excellent results in almost all of the subjects so treated. One must consider these results to be a type of synergism inasmuch as these superior results cannot be achieved by any of the individual components alone.

The compositions of the present invention are applied according to the following general regimen. In the case of the formulation of example 1, the composition was applied two to three times daily to the areas to be bleached. The composition is preferably applied three times a day for two days, then two times a day till irritation (mild inflammation) can be seen. Depending upon the degree of irritation, the composition is applied once or twice a day till depigmentation occurs. Depigmentation usually begins to occur five to twenty-one days after the initial application. Depigmentation is usually complete within six to ten weeks.

In patients with recurrent hyperpigmentation (negroes, other dark-skinned races,) pigmentation can be maintained by several applications per week.

The results produced by the application of the above composition are exceptionally good. In almost 100% of the subjects so treated, good to excellent depigmentation was obtained. The results were particularly dramatic in normal negro skin, wherein the skin was bleached white in the majority of subjects so treated.

Generally, similar results can be obtained with any of the formulations of the present inventions, although the frequency of application, the time required for depigmentation and the degree of depigmentation will vary with the components strength, and pharmaceutical vehicle used.

Examples of the Embodiments

Example 1

Hydroquinone	2%
Retinoic Acid	0.05%
Fluorometholone	0.025%
Fragrance q.s.	
Propylene glycol	
Ethanol (95%) aa q.s. ad 100 ml.	

Finely pulverize the hydroquinone, retinoic acid and fluorometholone and dissolve in about 80 ml. of the 50:50 mixture of propylene glycol and ethanol. Add the fragrance and q.s. ad to 100 ml. Mix well and apply to area to be bleached.

Example 2

Substitution in the formula of example 1 for the fluoro-

metholone used therein of 0.025% of dexamethasone produces an equivalent formulation.

Example 3

Hydroquinone	2%
Retinoic acid	0.05%
Fluorometholone	0.025%
Vanishing Cream base q.s. ad 100 gm.	

Finely pulverize the hydroquinone, retinoic acid and fluorometholone. Add a small quantity of the vanishing cream base and mix well to obtain a gritless paste. Add additional vanishing cream base to make 100 gm. of product. Mix well and apply.

Example 4

Hydroquinone	2%
Retinoic acid	0.05%
Fluorometholone	0.025%
Emolient lotion q.s. ad 100 ml.	

Finely pulverize the hydroquinone, retinoic acid and fluorometholone. Add a small quantity of the emolient lotion to the powder to make a gritless paste. Add sufficient lotion to make 100 ml. Mix well and apply.

Example 5

Hydroquinone	2%
Retinoic acid	0.05%
Hydrocortisone	2.5%
Vanishing cream base q.s. ad 100 gm.	

Prepare as in example 3.

Example 6

Hydroquinone	2%
n-Octylamine	0.5%
Fluorometholone	0.025%
Vanishing cream base q.s. ad 100 gm.	

Finely pulverize the hydroquinone and fluorometholone. Add the n-octylamine and a small quantity of vanishing cream to make a gritless paste. Add sufficient vanishing cream to make 100 gm. Mix well and apply.

Example 7

Hydroquinone	2%
Sodium lauryl sulfate	5%
Fluorometholone	0.025%
Vanishing cream base q.s. ad 100 gm.	

Prepare as in example 3.

Example 8

Hydroquinone	2%
Linoleic acid	50%
Fluorometholone	0.025%
Propylene glycol	
Ethanol (95%) BP q.s. ad 100 ml.	

Prepare as in example 1.

Example 9

Hydroquinone	2%
Linolenic acid	55%
Fluorometholone	0.025%
Propylene glycol	
Ethanol (95%) BP q.s. ad 100 ml.	

Prepare as in Example 1.

Example 10

Hydroquinone	2%
Arachidonic Acid	10%
Fluorometholone	0.025%
Propylene glycol	
Ethanol (95%) BP q.s. ad 100 ml.	

Prepare as in example 1.

Example 11

Hydroquinone	2%
Polyoxyethylene lauryl ether	10%
Fluorometholone	0.025%
Propylene glycol	
Ethanol (95%) BP q.s. ad 100 ml.	

Prepare as in example 1.

Example 12

Hydroquinone monobenzyl ether	5%
Retinoic acid	0.05%

Fluorometholone 0.025%
Vanishing cream base q.s. ad 100 gm.

Prepare as in example 3.

Example 13

Hydroquinone 5%
Retinoic acid 0.05%
Fluorometholone 0.05%
Vanishing cream base q.s. ad 100 gm.

Prepare as in example 3.

The above examples are illustrative of some of the variations in formulation that can be made within the scope of the present invention.

To prepare a more elegant or stable product, it may be desirable to incorporate fragrances, pigments, preservatives and/or a stabilizer including anti-oxidants, all of which are within the ability of those knowledgeable in the art.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A synergistic skin-bleaching composition for external application which comprises a mixture of 1% to about 10% of a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monethyl ether and hydroquinone monobenzyl ether, about 0.025% to about 1% of retinoic acid as a skin irritant-exfoliating agent, and about 0.01% to about 3.0% of an anti-inflammatory corticosteroid, formulated in a pharmaceutically-cosmetically acceptable vehicle.

2. A composition of claim 1 comprising about 1% to about 5% of a bleaching agent selected from the group comprising hydroquinone, hydroquinone monomethyl ether, hydroquinone monomethyl ether and hydroquinone monobenzyl ether, about 0.025% to about 1% of retinoic acid and about 0.01% to about 3.0% of an anti-inflammatory corticosteroids selected from the group comprising hydrocortisone, cortisone, prednisolone, prednisone, dexamethasone, betamethasone, fluocinolone acetonide, triamcinolone, fluocinolone, triamcinolone acetonide, methylprednisolone, fluoromatholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.

3. A composition of claim 1 comprising about 1% to about 5% of hydroquinone, about 0.020% to about 10% of retinoic acid as an skin-irritant-exfoliating agent, and about 0.01% to about 3% of an anti-inflammatory corticosteroid selected from the group comprising dexamethasone, betamethasone, flucinoline, flucinolone acetonide, triamcinolone, hydrocortisone, triamcinolone acetonide, fluoromatholone, or an ester thereof when chemically possible, formulated in a pharmaceutically-cosmetically acceptable vehicle.

4. A composition of claim 1 comprising about 2% hydroquinone, about 0.05% retinoic acid and 0.025% fluorometholone formulated in a pharmaceutically-cosmetically acceptable vehicle.

5. A composition of claim 1 comprising about 2% hydroquinone, about 0.05% retinoic acid and 0.025% dexamethasone formulated in a pharmaceutically-cosmetically acceptable vehicle.

6. A composition of claim 1 comprising about 2% hydroquinone, about 0.05% retinoic acid and about 2.5% hydrocortisone or hydrocortisone acetate formulated in a pharmaceutically-cosmetically acceptable vehicle.

7. A composition as in claim 1 or 2, comprising hydroquinone, retinoic acid, and an anti-inflammatory corticosteroid.